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(54)【発明の名称】 粉末製剤用ゴム栓

(57)【要約】

【課題】 第12改正日本薬局方、輸液用ゴム栓試験に適合し、かつ抗生物質等の製剤を常圧、または減圧、真空バイアル内で保存中に、用時溶解時に変色、混濁、沈殿等の原因となるゴム栓からの揮発物質をなくし、長期保存でも製剤の変質を起こさない性能を有する粉末製剤用ゴム栓の提供。

【解決手段】 イソブチレン(1B)パラメチルスチレン(PMS)の共重合体に臭素を付加させたポリマーを主成分に無機捕強剤が5~60重量部、精製塩素化ポリエチレンを20重量部以下、平均分子量が1,000以下の液状イソブチレンを2~10重量部配合して、加硫成形する。

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## DETAILED DESCRIPTION

### [Detailed Description of the Invention]

#### [0001]

[The technical field to which invention belongs] This invention relates opening of the vial which consists powder tablets, such as a medical-application container, especially an antibiotic, of an ordinary pressure or glass which carries out reduced pressure preservation, synthetic resin, etc. to seal and improvement of the rubber stopper for a powder tablet which carries out a detent plug. Without making structure of a rubber stopper into two-layer structure like the former, by using the polymer of specific composition for the rubber stopper itself, there is no quality of volatile matter in the bottom of reduced pressure, and it is related with the rubber stopper for a powder tablet which is moreover excellent in a moldability, cheap-boils and can be offered.

#### [0002]

[Description of the Prior Art] Conventionally, the rubber stopper which makes a principal component isobutylene isoprene rubber (IIR), polyisoprene rubber (IR), butadiene rubber (BR), an ethylene propylene rubber (EPM, EPDM), silicone rubber (SiR), an elastomer, etc. is used considering opening of the vial which saves powder tablets, such as an antibiotic, as a rubber stopper seal and for carrying out a detent plug and maintaining the airtightness inside interception or the vial for a tablet from oxygen, carbon dioxide gas, a steam, etc. in exterior air.

[0003] If the store method to the vial of a powder tablet is explained, holding [ being filled up with powder tablets, such as an antibiotic for injection of the specified quantity, in the vial, putting this in in a warehouse where opening of the vial is carried out, and ] the inside of a warehouse to an ordinary pressure or a vacuum, a rubber stopper will be pressed with a press board

and the state of all capping and nothing plugging will be completed. Then, it takes out from the inside of a warehouse, the volume bundle of the aluminium cap is put and carried out to a rubber stopper, and opening of the vial is sealed.

[0004] Although it is divided into the foot 12 in contact with the capping 11 on top and the tablet by the side of an inferior surface of tongue as the rubber stopper 10 for a powder tablet is shown in drawing 5 and drawing 6 on structure, the soft rubber of a capping 11 is another quality of the material, and the quality of the material of a foot 12 consists of material with more little quality of volatile matter. However, an antioxidant, an unreacted object, and oligomer (high-boiling point hydrocarbon matter) are contained in these rubber stoppers in process of raw material rubber manufacture. Moreover, in the rubber stopper, a \*\* sulfur compound, a wax, etc. which are blended in case vulcanization fabrication is carried out are contained simultaneously. Therefore, the matter contained in these rubber stoppers volatilizes during preservation within the vial filled up with the tablet, the antibiotic of cephalosporin and penicillins etc. is adsorbed in this quality of volatile matter, and the cause and bird clapper of transformation of a tablet, for example, turbidity, and precipitation are checked.

[0005] Moreover, in order that tablets, such as an antibiotic, may raise storage stability, it saves in many cases by making the inside of the vial reduced pressure, and under such a situation, since the quality of volatile matter increases increasingly, various problems will be started. then, it is shown in drawing 7 -- as -- the capping 11 of a rubber stopper 10, and a foot -- the foot which constitutes the 12 quality of the material from soft rubber, and contacts a tablet -- there is composition which carried out RAMINE \*\* of the 12 front face with the films 17, such as a fluororesin, polyethylene, and polypropylene

[0006] Furthermore, the saving method by the freeze vacuum drying is adopted as a store method for holding tablets, such as an antibiotic, with high quality for a long period of time. if it explains in full detail -- the inside of the vial -- medical fluids, such as an antibiotic for injection of the specified quantity, -- being filled up -- the inside of opening of the vial -- the steam of a medical fluid -- a passage -- being easy -- as -- the leg -- opening -- having prepared -- a rubber stopper -- half--- after capping, this is put in in a freeze vacuum-drying warehouse, and the inside of a warehouse is held on predetermined temperature and vacuum conditions

[0007] Although preservation conditions change with kinds of medical fluid Generally as freeze vacuum-drying conditions in a

warehouse, it holds to the temperature of -30 degrees C - -45 degrees C, a degree of vacuum 1 - 0.03Torr. It holds the temperature of -20 degrees C - +40 degrees C as primary dryness after freeze drying of 1 - 4 hours for 12 to 72 hours. further as secondary dryness If it holds for 1 to 6 hours and the moisture in the vial is removed from opening of the aforementioned leg of a rubber stopper the temperature of 30 degrees C - 60 degrees C, the tablet of the letter of a powder crystal will remain into the vial.

[0008] After a freeze vacuum drying, holding to a vacuum in a warehouse, a rubber stopper is pressed with a press board, the state of all capping and nothing plugging are completed, after that, it takes out from the inside of a warehouse, and an aluminium cap is put on a rubber stopper, a volume bundle is carried out, opening of the vial is sealed, and a freeze vacuum-drying tablet is obtained.

[0009] Conventionally, although isobutylene isoprene rubber (IIR) has mainly been used abundantly as a principal component, the rubber stopper for a powder tablet Composition of this isobutylene isoprene rubber (IIR) is the polymer which carried out copolymerization of the isoprene to the isobutylene one to 5% of the weight. The chlorinated butyl rubber which added chlorine to this isobutylene isoprene rubber in addition to this at the copolymer of an isobutylene and an isoprene, There is bridge formation isobutylene isoprene rubber which added the brominated butyl rubber which added the bromine, and the divinylbenzene, and it has the property as rubber stoppers for a powder tablet, such as low gas permeability, low-water-flow part permeability, thermal resistance, an aging resistance, and chemical resistance, respectively.

[0010] i-butene for C4 \*\* by which separation refining of the manufacture method of these isobutylene isoprene rubber is carried out from extractive distillation in the manufacture process of a high octane value cracked gasoline (petroleum naphtha),

The isoprene for C5 \*\* in which separation refining was similarly carried out by extractive distillation can be mixed 1 to 5%, an aluminum chloride can be added to a polymerization catalyst, the inside of a reaction vessel is made into -95--98 degree C, after carrying out a stirring reaction, moisture and an unreacted object can be removed and isobutylene isoprene rubber (IIR) can be obtained.

[0011] However, in order that a part of isoprene may act as a terminator at the time of the polymerization of an isobutylene and an isoprene, the short oligomer (high-boiling point hydrocarbons C16-C30) of the chain which the child and the isoprene

combined several little unreacted object and isobutylene minutes in the copolymer remains. that is, matter, such as oligomer, volatilizes to the tablet where the rubber stopper for a powder tablet which made the principal component the isobutylene isoprene rubber (IIR) which copolymerized the isoprene in the isobutylene was saved under reduced pressure in the vial, and it sticks to it -- having -- transformation of a tablet, for example, business, -- the time -- the time of the dissolution -- turbidity -- starting -- a cause -- becoming -- being easy .

[0012] Conventionally, making a rubber stopper into the two-layer structure at JP, 62-13627, B is proposed as a rubber stopper for a freeze vacuum-drying tablet which has improved the fault which causes trouble to the stability of transformation or quality in contact nature with the tablet which the rubber stopper quality of the material has. Namely, although a rubber stopper 10 is divided into the foot 12 which contacts the capping 11 on top and the tablet by the side of an inferior surface of tongue on structure as shown in drawing 8 and drawing 9 It consists of a rubber constituent by which blended adsorbents, such as activated carbon and silica gel, and vulcanization fabrication was carried out with a capping 11 and another quality of the material, the quality of the material of a foot 12 makes it adsorb, while composing volatile matter, such as decomposition oligomer under composition, a sulphur-containing compound, and a fatty acid, and it consists of composition which prevents volatilization of the matter constituting the cause of transformation of a tablet. In addition, 13 in drawing is the ring section and 14 is a height for half-capping.

[0013] moreover, the inferior surface of tongue which constitutes the capping 11 of the upper surface of a rubber stopper 10 in JP, 63-43104, B from soft rubber, and contacts it with a tablet as shown in drawing 10 -- a foot -- it considered as the two-layer structure which constituted the 15 quality of the material from an inactive fluororubber, and the quality of volatile matter from the soft rubber of a capping 11 is prevented

[0014] furthermore, JP, 52-1335, B, JP, 54-9119, B, JP, 57-53184, B, JP, 4-22362, A, and JP, 5-64062, B each official report -- setting -- the capping 11 of a rubber stopper 10, and an inferior surface of tongue -- a foot -- the foot which constitutes the 16 quality of the material from soft rubber, and contacts a tablet -- RAMINE \*\* of the 16 front face is carried out with the films 17, such as a fluororesin, polyethylene, and polypropylene, and the lamination rubber stopper which consists of composition which intercepts the quality of volatile matter from the inside of a rubber stopper constituent is proposed

[0015]

[Problem(s) to be Solved by the Invention] a medical-application container rubber stopper -- setting -- transformation of a tablet, for example, business, -- the time -- the time of the dissolution -- with the above-mentioned conventional technology adopted in order to prevent discoloration, turbidity, precipitation, etc. Composition consists of the two-layer structure which laminates the soft rubber quality of the material of an upper surface capping, the special rubber quality of the material by the side of an inferior surface of tongue, or a resin film, and all have the very complicated forming cycle of a rubber stopper. And it is difficult not to avoid product dispersion, since there are many processes, but to secure the stability of the quality as a medical-application rubber stopper. Furthermore, the fluororubber or fluororessin of the inferior-surface-of-tongue quality of the material had the problem which cannot offer a rubber stopper cheaply by requiring a comparatively expensive thing and a great man day.

[0016] Moreover, it is required that the character which passes the rubber stopper examination specification for the Pharmacopoeia of Japan transfusion should be provided as well as the need that the rubber stopper concerned satisfies the low gas and low-water-flow part permeability which are demanded as a medical-application rubber stopper, good airtightness, \*\*\*\*\*\*, thermal resistance, an aging resistance, coring nature, etc.

[0017] This invention satisfies many properties and the rubber stopper examination specification for the Pharmacopoeia of Japan transfusion demanded as a medical-application rubber stopper, and loses the quality of volatile matter from a rubber stopper, and its moldability is good and it usually aims at offer of the rubber stopper for a powder tablet which consists of composition which can be offered cheaply at a still easier process for the purpose of storage of tablets, such as powder and freeze-drying powder, especially offer of the rubber stopper which can raise the storage stability under reduced pressure.

[0018]

[Means for Solving the Problem] In order that artificers may solve an above-mentioned technical problem, raw material polymer, a modifier, As a result of examining many things about the kind of various compounding agents, and its loadings, the polymer which made the bromine add to the copolymer of an isobutylene (IB) and PARAME chill styrene (PMS) is made into a principal component. By using for the rubber stopper for a powder tablet the polymer of the composition which furthermore

blends a refining chlorinated-polyethylene, liquefied isobutylene, and inorganic reinforcing agent The quality of volatile matter from the rubber stopper which causes transformation of a tablet by the inside of a container reduced pressure and when high-vacuum-izing further and saving especially is removed completely. The knowledge of the ability to provide [ having the conventional quality which could carry out vulcanization fabrication of the configuration with various freeze-dried types, vial types, transfusion types, etc. easily much more like the mold rubber stopper, and was very excellent, and sanitation nature, and ] more simply [ a process ] than the rubber stopper of the conventional two-layer structure and cheaply was carried out, and this invention was completed.

[0019] Ethylene-propylene rubber applied as a medical-application rubber stopper in order to solve the conventional problem, if it explains in full detail (it EPM(s)) EPDM, butadiene rubber (BR), polyisoprene-rubber (IR) styrene-butadiene rubber (SBR), Silicone rubber (SiR), shrimp chlorhydrin rubber (CO.ECO), The result wholeheartedly studied about the fluororubber (FM), an isobutylene, the poly methyl-styrene copolymer, etc., The low gas permeability which is the property of the isobutylene conventionally used as a rubber stopper for a powder tablet, and an isoprene copolymer (IIR), performances, such as low-water-flow part permeability, thermal resistance, and an aging resistance, -- having -- in addition -- and transformation and business of a tablet -- the time -- the time of the dissolution -- the polymer which added the bromine to the copolymer of the isobutylene which does not contain the high-boiling point hydrocarbon of the carbon numbers C16-C30, such as oligomer

leading to turbidity, and the poly methyl styrene was found out

[0020] The isoprene in the isobutylene used as the cause which generates the oligomer leading to turbidity etc., and an isoprene copolymer (IIR) is perceived. namely, transformation of a tablet, for example, business, -- the time -- the time of the dissolution -- Without replacing with this isoprene and acting as a terminator at the time of a polymerization with an isobutylene The poly methyl styrene which is made to activate polymerization reaction and does not generate oligomer etc. is made into a copolymer. Furthermore, the polymer suitable for the rubber stopper for a powder tablet which was made to add a bromine to this copolymer and made vulcanization fabrication easy was found out, the knowledge of the optimal rubber stopper for carrying out the mothball of the tablet under a high vacuum being obtained was carried out, and this invention was completed.

[0021] That is, this invention is a rubber stopper for a powder tablet which makes a principal component the polymer which made the bromine add to the copolymer of an isobutylene (IB) and PARAME chill styrene (PMS), and makes a principal component the polymer which made the bromine add to the copolymer of an isobutylene (IB) and PARAME chill styrene (PMS), and proposes the rubber stopper for a powder tablet which comes to blend a refining chlorinated polyethylene below 20 weight sections.

[0022] In the rubber stopper for a powder tablet of the above-mentioned composition, this invention carries out 5-60 weight section combination of the inorganic reinforcing agent, and carries out vulcanization fabrication. Moreover, a bird clapper, An inorganic reinforcing agent carries out 2-10 weight section combination of 5 - 60 weight section and the liquefied isobutylene, and carries out vulcanization fabrication. A bird clapper, For the percentage of polymer, PARAME chill styrene (PMS) is [ 5 - 7.5 % of the weight and a bromine ] 0.8 - 2% of the weight of ranges about an isobutylene (IB) at a principal component, The rubber stopper for a powder tablet with which a liquefied isobutylene is characterized by average solution viscosity being 30 or less PA-S in 1000 or less average molecular weight, respectively is proposed collectively.

[0023]

[Embodiments of the Invention] Although this invention is limited to the polymer which added the bromine to the isobutylene and the PARAME chill styrene copolymer as a principal component which was usually suitable for the performance as an ordinary pressure or reduced pressure, and a rubber stopper for containers further saved under a high vacuum in various powder tablets, such as a granulatio tablet by dryness, and a powder tablet or a powder tablet by the freeze vacuum drying, it shows the typical example of a performance of this polymer in Table 1.

[0024]

[Table 1]

[0025] In this invention, the combination composition ratio which makes an isobutylene and a PARAME chill styrene copolymer a principal component carries out to more than 70 weight sections, in addition does not have the quality of volatile matter as a modifier, and mixes a refining chlorinated polyethylene, epichlorohydrin rubber (CO.ECO), super-macromolecule polyethylene, a liquefied isobutylene, etc. the making prevention of the roll kneading nature of the copolymer of an

isobutylene and the poly methyl styrene, a vulcanization moldability, and a precurve, other processability, etc. improve purpose.

[0026] Especially a refining chlorinated polyethylene has the improvement of non-adhesiveness at the time of roll processing, the dimensional stability at the time of preforming, and the effect of the deformation prevention at the time of vulcanization fabrication. Moreover, while an addition increases as loadings, in order that hardness may become high, crosslinking density may fall and gas and moisture permeability may spoil the property as a large next door and a rubber stopper for a powder tablet, the combination below 20 weight sections is desirable, and is 5 - 15 weight section desirably. The rinse of the refining chlorinated polyethylene used for this invention is carried out with an organic solvent, for example, ketones, and alcohols, it removes the fatty acid in a constituent, and other impurities, and raises the degree of refining.

[0027] Also in the above modifier, especially a liquefied isobutylene lowers the viscosity of a rubber combination constituent, improves the fluidity of the rubber ground at the time of vulcanization fabrication, prevents the precurve of a constituent, has the property of raising storage stability, also has neither bleeding development nor solvent extraction like a petroleum system plasticizer, and also has few falls of physical properties. The liquefied isobutylene used here is average molecular weight 1,000. Average solution viscosity is [ the following and ] as follows [ 30Pa.s ]. Moreover, there is also no quality of volatile matter demanded as a rubber stopper for a powder tablet, and it excels in low gas permeability, low-water-flow part permeability, the aging resistance, etc.

[0028] The loadings to the isobutylene and the poly methyl-styrene copolymer of a liquefied isobutylene are 2 - 10 weight section, in under 2 weight sections, it does not see, but above 10 weight sections, crosslinking reaction is checked conversely, rubber elasticity falls, the airtightness of a rubber stopper, deformation, and surface adhesiveness become high, and the fluidity of the ground at the time of vulcanization fabrication of a constituent and the prevention effect of a precurve are unsuitable as a rubber stopper for a powder tablet.

[0029] As a minerals reinforcing agent, clay, a barium sulfate, talc, a silica, and silica gel are used. Clay and talc are used as a general reinforcing agent also in it, and silica gel etc. is effective as an adsorbent of the quality of volatile matter in a combination constituent. Although combination of 5 weight sections is required for them if there are few inorganic reinforcing

agents in order to acquire the effect Since the viscosity of a combination constituent becomes high too much, the fluidity at the time of vulcanization fabrication becomes bad and deformation of vulcanization mold goods and hardness become high in combination exceeding 60 weight sections, Since coring at the time of \*\*\* tends to happen, and heavy metal, such as lead and cadmium, contains in reinforcing materials, such as clay, and it becomes unsuitable in the rubber stopper examination for Japanese Pharmacopoeia and transfusion, it considers as combination of 5 - 60 weight section. Desirable loadings are 10 - 50 weight section.

[0030] As a vulcanizing agent, there are a triazine thiol system, an organic sulfur system, an amine system, and a silane coupling agent, and the loadings are 0.2. It is -3 weight section. As a vulcanization activity assistant, there are a zinc oxide, a magnesium oxide, a zinc stearate, a synthetic hydrotalcite, etc., and the loadings are 0.2. It is -5 weight section. As a coloring agent, there are titanium oxide, carbon black, rouge, an organic pigment, etc., and the loadings are 0.01 - 5 weight section.

[0031]

[Example]

The regular isobutylene isoprene rubber and the chlorinated butyl rubber which are the principal component of the conventional rubber stopper constituent for a powder tablet are explained as one or less example and an example of this invention as the polymer which makes an isobutylene and the poly methyl-styrene copolymer a principal component, and an example of comparison. According to the recipe of each example shown in Table 2, and the example of comparison, weighing capacity of the compounding agents, such as raw material rubber, a vulcanizing agent, and an inorganic reinforcing agent, is carried out, and it mixes uniformly under the temperature of 90 degrees C - 120 degrees C, and the conditions for time 15 minutes by the sealing pressurization type kneader (product made from TOUSHIN, Inc.). Then, it took out from the pressurized kneader; the vulcanizing agent was added with an open roll, and the unvulcanized-rubber sample for an examination was created.

[0032]

[Table 2]

[0033] The manufacturer of the medicine in Table 2 is as follows.

(1) EKUSUPURO, EMDX 93-5 Product made from Exxon Chemistry (2) MDB87-I Product made from Japanese Butyl (3) HT 10-66

Product made from Exxon Chemistry (4) JISUNETTOF Made in 3 \*\* Chemicals (5) ARUKA mizer 1 Product made from Consonance Chemical industry (6) SH6062 Product made from Toray Dow Corning Silicone (7) Nocceler BZ Product made from Ouchi Shinko Chemical Industry (8) BAL tuck No. 5 made in Elf Atochem Japan (9) Nip seal VN-3 Product made from Japanese Silica Industry (10) ST kaolin Product made from Tsuchiya Kaolin (11) Oppanol B-3 Basf Japan make (12) DAISO rack H-135 DAISO Co., Ltd. make [0034] Vulcanization of the unvulcanized-rubber sample for an examination was created according to SRIS-3603, and the physical examination of vulcanized rubber was performed according to vulcanized-rubber physical-test method JIS.K-6301. Moreover, the viscosity and precure time measurement of an unvulcanized-rubber sample are also performed, and the result is shown in Table 3.

[0035] It turns out that the hardness of the vulcanization article of a triazine thiol system is also high as shown in the result of the example 1 of Table 2, and the example 1 of comparison, and tensile strength is also high. Compared with the vulcanization article of an organic sulfur system, crosslinking density shows the bird clapper highly and this has it. [advantageous to vulcanization fabrication of a rubber stopper] However, the effect that the viscosity of a non-vulcanized constituent also becomes low and precure time becomes long compared with an organic sulfur system by being in the inclination for precure time to be early, and adding a liquefied isobutylene in the example 2 is seen, and the constituent of a triazine thiol system shows that storage stability increases.

[0036]

[Table 3]

[0037] an example 2 -- the rubber stopper for a powder tablet usual in the rubber stopper 1 by this invention -- drawing 1 -- moreover, as shown in drawing 3, the foot 3 and the ring section 4 in contact with the capping 2 on top and the tablet by the side of an inferior surface of tongue, and the height 5 for half-capping also consist of the same polymer altogether, and unification fabrication of the rubber stopper for a freeze vacuum-drying tablet is carried out An eluting material test is performed according to the rubber stopper examination for the 12th revision Pharmacopoeia of Japan transfusion, and shows the result in Table 4. A volatile-matter examination puts one silica gel into the vial 6 shown in drawing 2 and drawing 4, and

carries out the reduced pressure seal detent plug of the rubber stopper 1 for an examination. After carrying out the passage of time of this for one month 50 degrees C in a thermostat, solvent extraction of the matter to which it stuck at silica gel is carried out, and the high-boiling point hydrocarbon in this extract is detected by the gas chromatograph. This result is shown in Table 5.

[0038] Although specification is altogether satisfied in an eluting material test as shown in the result of the examples 1-4 of Table 4, and the examples 1-3 of comparison, when a bridge is constructed by the triazine thiol system in examples 1-3 and the example 1 of comparison, there is also no zincky detection, and compared with organic sulfur bridge formation, there are also few values of a ultraviolet absorption spectrum and it is it is low and advantageous [ values / an effluent ] as the bridge formation method.